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Secular Trends in Breast Cancer Risk among Women with HIV Initiating ART in North America

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Abstract

Background: Studies suggest lower risk of breast cancer in women with versus without HIV. These estimates may be biased by lower life expectancy and younger age distribution of women with HIV. Our analysis evaluated this bias and characterized secular trends in breast cancer among women with HIV initiating ART. We hypothesized breast cancer risk would increase over time as mortality decreased.

Setting: Women with HIV prescribed ART in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) from 1997–2016.

Methods: We estimated breast cancer hazard (cause-specific hazard ratios [csHR]) and cumulative incidence accounting for competing risks (subdistribution hazard ratios [sdHR]) to

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assess changes in breast cancer risk over time. This was assessed overall (1997–2016) and within/across calendar periods. Analyses were adjusted for race/ethnicity and inverse probability weighted for cohort. Cumulative incidence was graphically assessed by calendar period and race/ethnicity.

Results: We observed 11,587 women during 1997–2016, contributing 63 incident breast cancer diagnoses and 1,353 deaths (73,445 person-years [median follow-up=4.5 years]). Breast cancer cumulative incidence was 3.2% for 1997–2016. We observed no secular trends in breast cancer hazard or cumulative incidence. There were annual declines in the hazard and cumulative incidence of death (csHR and sdHR: 0.89, 95% CI 0.87, 0.91) which remained within and across calendar periods.

Conclusion: These findings contradict the hypothesis of increasing breast cancer risk with declining mortality over time among women with HIV, suggesting limited impact of changing mortality on breast cancer risk. Additional inquiry is merited as survival improves among women with HIV.

Keywords

women with HIV; breast cancer trends; mortality; North America

INTRODUCTION

People with HIV (PWH) in the United States have made substantial gains in life expectancy, although disparities within this population by sex, race/ethnicity, and HIV acquisition risk group persist.[1–3] As this population ages, with the majority now >50 years of age,[4] PWH are increasingly at risk for common chronic comorbidities seen in the general population, including non-AIDS defining cancers (NADCs).[5,6] Over time, the cancer burden has shifted from predominantly AIDS-defining cancers to NADCs.[7–10] The mechanisms driving this shift are likely multifactorial, and differential by cancer site/type. Potential factors include population-level aging, risk factor prevalence (e.g. smoking), human papillomavirus/other coinfections, and immune suppression.[11–14]

Some studies suggest the risk of breast cancer in women with HIV is lower compared to women in the general population,[15–17] despite the high prevalence of obesity and alcohol abuse in women with HIV,[18,19] and chronic inflammation associated with long term infection, which are relevant risk factors for breast cancer. In the HIV/AIDS Cancer Match study (HACM), two analyses found protective effects of HIV infection on breast cancer: standardized incidence ratio (SIR) 0.69 (95% CI 0.63, 0.7) in 1980–2002,[16] and SIR 0.63 (95% CI 0.58, 0.68) in 1996–2012.[15] A third study found a reduced risk of breast cancer from 1992–1995 (standardized rate ratio [SRR]=0.70, 95% CI 0.30, 1.90), and a null effect from 2000–2003 (SRR=1.10, 95% CI 0.70, 1.80).[17]

Observational studies cast doubt on racial and age differences between women with versus without HIV as drivers of these associations. Though women with HIV have a younger age distribution, and are predominantly Black[20] (among whom breast cancer risk is lower compared to white women)[21,22], prior estimates account for these factors.[15–17] Also, the

racial disparity in breast cancer risk in the general population by race is narrowing.[22] Differences in screening has also been postulated as explaining this disparity.[23–25] Though research is sparse, one study found mammography use was comparable by HIV status.[26] Another study found stage at diagnosis did not differ by HIV status, indicating comparable detection.[25]

The changing mortality rate among women with HIV from early treatment eras to the modern ART era could also lead to artificially lower rates of disease. Specifically, it is unclear whether the previously documented low risk of breast cancer might be attributed to the younger age distribution of women with HIV relative to the general population, where breast cancer risk is typically not elevated, and/or that women with HIV had a lower life expectancy compared to women in the general US population.[3] Though prior studies have used age-standardization to mitigate this bias, analyses addressing breast cancer risk in older women with HIV have not addressed the competing risk of death, which would allow for a more complete understanding of trends in breast cancer among women with HIV.[12]

Thus, the objectives of our study were to: 1) characterize breast cancer risk over calendar time in the context of changes in mortality; and 2) evaluate the role of the potential bias produced by changing mortality (shifts in the age distribution and increased life expectancy) in breast cancer risk among women with HIV who have initiated ART.

METHODS

Study Population

The study population included women with HIV participating in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD).[27] Briefly, the NA-ACCORD is a consortium of single- and multisite cohorts of adults with HIV in the U.S. and Canada. Individuals are eligible for inclusion if they attended two or more HIV care visits within twelve months (i.e. they successfully linked into HIV care). Each cohort employs standardized data collection, submitting data on enrolled participant characteristics, diagnoses, laboratory measures, prescribed medications, and vital status to the Data Management Core (University of Washington, Seattle, WA). Data are harmonized across cohorts and evaluated for quality control prior to being transmitted to the Epidemiology/ Biostatistics Core (Johns Hopkins University, Baltimore, Maryland).

Cis-gender women were included in our nested study if they were ≥18 years old, prescribed ART, under observation for at least six months from 1996 through 2016, had no history of any cancer (including non-melanoma skin cancer), and had data available on race/ethnicity. This excluded 224 first-time AIDS-defining cancer diagnoses, 1 was subsequently diagnosed with breast cancer, and 93 died. Twenty NA-ACCORD cohorts provided data on women meeting these criteria. Although women could enter as early as 1996, person-time and events prior to 1997 were excluded due to limited observation during this year (Figure 1).

Outcome: Breast Cancer

First-time breast cancer diagnosis was ascertained and validated using a standardized abstraction protocol as described elsewhere.[12] Abstraction included manual review of

medical charts and pathology reports for cancer site and histopathology, and/or linkages with cancer registries.

Death

Deaths in the NA-ACCORD are ascertained via linkages with: 1) provincial, state, or national death registries (includes the US National Death Index Plus), 2) medical record abstraction following notification of death to the attending physician, 3) outreach to family and/or friends, and 4) monitoring of obituaries. Though cohorts participating in the NA-ACCORD have differing methods of ascertainment, mortality rates are comparable between cohorts with and without registry linkages.[28] Lags in death index matching were accounted for by administratively censoring women at December 31st 2016. Death was defined as all-cause mortality.

Covariates of interest

Age was estimated from year of birth. Race/ethnicity was categorized as: Non-Hispanic Black, non-Hispanic white, Hispanic, or other race/ethnicity. This was selected to reflect racial/ethnic differences in breast cancer risk observed in the general population,[22] as well as racial/ethnic differences in mortality among women with HIV.[4] This also ensured large enough sample size for stable estimates, and is consistent with the literature on breast cancer risk in women with HIV.[15] Antiretroviral therapy (ART) exposure was defined using the first occurrence of a prescription for effective antiretroviral therapy for at least 30 days; effective antiretroviral therapy was defined using treatment guidelines.[29]

Statistical Analyses

Women contributed person-time and events beginning 6 months after the latest of the following dates: January 1st, 1996, enrollment into the NA-ACCORD, age 25, ART initiation date, or cohort-specific cancer validation start date. The six-month period following the start date was added to mitigate including prevalent breast cancer diagnoses and to exclude immortal person-time.[30,31] Women exited the analysis on the earliest of the following dates: incident breast cancer diagnosis, death, administrative censoring on December 31st, 2016, cohort-specific cancer validation end date, or loss-to-follow-up. Loss-to-follow-up was defined as the last encounter prior to a two-year gap in either CD4 count or HIV viral load laboratory measurements. The timescale for this analysis was age, allowing women of the same age to be compared by calendar period with respect to risk of breast cancer or death, effectively controlling for the influence of age on breast cancer risk.

To characterize secular changes in the risk of breast cancer, we estimated cause-specific hazard ratios (csHR) and sub-distribution hazard ratios (sdHR) for the association between time-updated calendar time and time to breast cancer. We also estimated the csHR and the sdHR for the association between calendar time and time to death. Comparisons of the csHRs and sdHRs for both breast cancer and death can elucidate the contribution of death to the hazard of breast cancer over time.[12] As described by Silverberg et al., in the era of effective ART, women with HIV are experiencing increased life expectancy over time. Assuming the competing risk of death is the only reason breast cancer risk appears lower in women with compared to without HIV, the hazard rate (the instantaneous risk of breast

cancer: csHR), may not vary over time, but the cumulative incidence (the risk of breast cancer given surviving to a certain time: sdHR) would be expected to increase as a result of decreased mortality.[12]

We also graphically assessed breast cancer and all-cause mortality rates over calendar time by plotting lowess smoothed incidence rates (the ratio of lowess smoothed annual breast cancer/death counts over lowess smoothed person-time [days] for each calendar year).

Proportionality of hazards was assessed using interaction terms between calendar year and age. Calendar year was modelled continuously (centered at 2006) to assess annual trends overall (1997–2016) and using linear splines to assess annual trends within time-updated calendar periods (1997–2001, 2002–2006, 2007–2011, and 2012–2016). Calendar periods approximated changes in ART treatment guidelines. We additionally assessed changes in breast cancer risk across calendar periods, comparing 1997–2001 to all later periods. All models were adjusted for race/ethnicity, and regression analyses were repeated additionally adjusting for having an AIDS-defining illness within a year prior to ART initiation (yes or no). Models were weighted as the inverse probability of being in each cohort (or subsite for multisite cohorts) to adjust for differences across cohorts. The cumulative incidence of breast cancer over age was graphically examined using non-parametric estimators accounting for the competing risk of death stratified by calendar period and race/ethnicity.

RESULTS

Characteristics of the Study Population

We included 11,587 women (Figure 1) contributing 73,445 person-years. There were 63 incident breast cancer diagnoses, and 1,353 deaths from 1997–2016, yielding a breast cancer incidence rate of 8.6 cases (95% CI 6.7, 11.0) per 10,000 person-years and mortality rate of 184.2 deaths (95% CI 174.7, 194.3) per 10,000 person-years (Table 1). The median age at analysis entry was 40.0 years (IQR: 33.5, 47.0 years), and median age at exit was 47.0 years (IQR: 39.1, 54.1 years). The median duration of follow-up for women was 4.5 years (IQR: 2.3, 9.5 years). Women were predominantly non-Hispanic Black (59.4%) and did not have an AIDS-defining illness in the year prior to ART initiation (91%) (Table 1). There was variability in the distribution of race/ethnicity over calendar year (average annual percent change ≤15% per category) and AIDS-defining illness in the year prior to ART (average annual percent change <10% per category) (results not shown).

Secular changes in cause-specific hazard of breast cancer and death

The cause-specific hazard assessed overall (1997–2016) for breast cancer was stagnant, and for death declined over time (Table 2). There was no change in the cause-specific hazard of breast cancer (csHR: 0.98, 95% CI 0.92, 1.05) per one-year increase in calendar year. There was a 11% decrease in the cause-specific hazard of death per one-year increase in calendar year (csHR 0.89, 95% CI 0.87, 0.91).

The cause-specific hazard was also assessed within calendar periods (Table 2). The cause-specific hazard of breast cancer within calendar periods did not significantly change over time and was characterized by modest fluctuation. This was also observed when comparing

breast cancer risk across calendar periods, where there was no significant difference in breast cancer hazard comparing later periods to 1997–2001. When visually assessing the rate of breast cancer over time using lowess smoothed incidence rates over calendar year, there was an initial small increase in breast cancer which peaked from 1997 to 2008, but little change was observed after this (Figure 2A).

There was a consistent decline in the hazard of death within calendar periods. In 1997–2001, there was a 11% decline per year in the hazard of death (csHR: 0.89, 95% CI 0.79, 1.00). In 2002–2006 there was an 8% annual decrease in the hazard of death (csHR: 0.92, 95% CI 0.85, 0.99), followed by a 16% decrease in the annual hazard of death in 2007–2011 (csHR: 0.84, 95% CI 0.77, 0.92). This stabilized in 2012–2016, with a non-significant 10% annual decline in the hazard of death (csHR: 0.90, 95% CI 0.77, 1.06). When evaluated across calendar periods, compared to 1997–2001, the risk of death significantly increasingly declined for 2002–2006 (csHR: 0.62, 95% CI 0.44, 0.87), 2007–2011 (csHR: 0.37, 95% CI 0.26, 0.51), and 2012–2016 (csHR: 0.16, 95% CI 0.11, 0.24). This was consistent with the lowess smoothed all-cause mortality rates by calendar year, where there was a steady decline in all-cause mortality with increasing calendar year (Figure 2B).

Secular change in cumulative incidence of breast cancer and all-cause death

The cumulative incidence of breast cancer (estimated via the breast cancer sdHRs) followed similar trends to the breast cancer csHRs (Table 2). There was no significant annual change in the cumulative incidence of breast cancer assessed from 1997–2016, within calendar period, or across calendar periods. The cumulative incidence of death followed a markedly similar pattern to the cause-specific hazard of death, characterized by an 11% annual decrease in the cumulative incidence of death (sdHR: 0.89, 95% CI 0.87, 0.91) and declines in the annual cumulative incidence of death in 1997–2001, 2002–2006, 2007–2011, and 2012–2016 of 11%, 8%, 16% and 10% (Table 2). Compared to 1997–2001, cumulative incidence of death was significantly lower with each increasing calendar period.

All regression analyses were repeated additionally adjusting for AIDS-defining illness in the year prior to ART, which did not substantively change estimates (results not shown).

Cumulative incidence of breast cancer by calendar period

The incidence of breast cancer fluctuated with calendar period. The overall cumulative incidence of breast cancer from 1997–2016 was 3.2% (95% CI 2.1%, 4.7%). The cumulative incidence of breast cancer was 2.3% (95% CI 0.1%, 6.2%) in 1997–2001, 2.3% (95% CI 1.2%, 3.9%) in 2002–2006, 4.5% (95% CI 2.1%, 8.4%) in 2007–2011, and 3.8% (95% CI 1.7%, 7.2%) in 2012–2016. Assessed graphically, there were no discernable patterns in breast cancer cumulative incidence with age as the timescale with respect to calendar periods (Figure 3A). There was limited follow-up beyond age 65, so estimates should be interpreted cautiously (Supplemental Figure 1).

Cumulative incidence was highest among Hispanic women at 4.7% (95% CI 1.5%, 11.1%), followed by non-Hispanic white women at 4.2% (95% CI, 1.7%, 8.4%), non-Hispanic Black women at 2.6% (95% CI, 1.5%, 4.3%), and women of other race/ethnicity at 0.1% (95% CI,

0.2%, 3.3%). There were no differences by race/ethnicity, until the end of follow-up, where the data are sparse (Figure 3B).

DISCUSSION

In a large sample of women with HIV prescribed ART in North America with no history of cancer, we found no trends in either the hazard or cumulative incidence of breast cancer over calendar time accounting for age (timescale), race/ethnicity, and cohort. The hazard and cumulative incidence of death demonstrated consistent declines over time when assessed from 1997–2016 and within/across calendar periods. Cumulative incidence of breast cancer was 3.2% over 16 years of follow-up in women with HIV initiating ART with no history of any cancer (median follow-up 4.5 years) for the years 1997–2016. There were no significant differences in breast cancer risk by calendar period or race/ethnicity.

These findings suggest a limited role of changing mortality on breast cancer risk among women with HIV initiating ART. Despite declines in mortality (as both the csHRs and sdHRs for death indicated), there was no impact of declining mortality on trends in breast cancer risk over time. If mortality substantively impacted breast cancer incidence among women with HIV, we would expect to see a pattern of increasing breast cancer cumulative incidence with increasing calendar year; however, we observed no difference in breast cancer cumulative incidence when stratified by calendar period.

Our results align with an analysis in HACM, which found that the annual percent change in breast cancer incidence rates did not change over time from 1996–2010.[8] Another study conducted in HACM projecting breast cancer incidence through 2030 found no change in the rate of breast cancer from 2006–2012.[32] To compare these findings to ours, one must assume the incidence rate is a reasonable estimate of the average hazard in these calendar periods; however, the incidence rate is not directly comparable to the hazard, cumulative incidence, or lowess incidence rates examined in this analysis. In the era of effective ART, our observation of declining mortality over calendar time has been well-documented among PWH.[33–35] This has been observed in women with HIV,[36] though in the US, relative to men the magnitude of this decline in mortality is smaller for women.[37]

Breast cancer incidence in this analysis is markedly lower than the commonly cited 12% lifetime risk among women in the general population.[38] There are substantial differences in the underlying populations that generated our estimate (women with HIV initiating ART with no history of cancer, and under observation in the NA-ACCORD), and those in the general population of women. Moreover, given the limited follow-up among women beyond age 65, and the increased risk of breast cancer in women 65 and older observed in the general population, our estimated risk likely does not reflect lifetime breast cancer risk in women with HIV. No direct comparisons should be made, though this notable disparity merits additional investigation. To our knowledge, breast cancer lifetime cumulative incidence has not been estimated in women with HIV initiating ART.

Our observations could be an artifact of the increasing number of women enrolling in the NA-ACCORD, entering the analysis (Supplemental Figure 1) and the integration of cancer

diagnosis observation into each cohort in later years. Cohorts/subsites enter and exit this analysis at varying timepoints according to when cohorts began participation in the NA-ACCORD and began capturing cancer diagnoses. It is possible that fluctuation in cohort participation over time could lead to differential cancer ascertainment over time, though models accounted for cohort/subsite. At the individual level, women enter and leave the study at different timepoints, and we assume that women who are lost-to-follow-up are represented by the women who remain.

We did not adjust for secular trends in factors related to breast cancer incidence such as changes in screening practices, guidelines, insurance coverage, risk factors for breast cancer (e.g. reproductive factors, alcohol abuse, obesity), or breast cancer risk in the general population due to limited data availability and sample size constraints. Therefore, we cannot isolate the effect of mortality alone on breast cancer risk over time. We assumed that the age-specific risk of cancer was constant by birth cohort (e.g. a 35-year-old woman with treated HIV in 1996 is comparable to a 35-year-old woman with treated HIV in 2007). We attempted to mitigate this bias by limiting our data to women who initiated ART and were under observation using a conservative definition of loss-to-follow-up. The small number of breast cancer cases (n=63) limited the precision of our estimates. We observed little follow-up among women older than 65, restricting our ability to assess lifetime breast cancer risk among women with HIV and may have led to under-ascertainment of cases. Lastly, by restricting to women without a history of cancer, we are selecting a healthier subset of women with HIV who have initiated ART, especially since AIDS-defining cancers were excluded. Therefore, findings may not be applicable to all women with HIV, where associations with calendar time may differ.

Our analysis adds to the existing limited literature on breast cancer among women with HIV using a large cohort of women with HIV accessing care and initiating ART in North America with moderate duration of follow-up and validated cancer diagnoses. This offers additional evidence that changing mortality is not a mechanism driving lower risk of breast cancer in women with compared to without HIV. This is a novel evaluation of breast cancer over time among women with HIV which assesses the competing risk of death. Further, by limiting our analyses to women initiating ART who are engaged in care (as per our loss-to-follow-up criteria), we minimized potential under ascertainment of outcomes.

The number of women living with HIV over age 50 will continue rising as life expectancy increases and mortality decreases. A rise in breast cancer incidence is plausible given that declining HIV-associated mortality has resulted in an older and aging population of women with HIV who are at the most risk for breast cancer. This was not supported by our findings where we saw no substantial change in breast cancer risk or cumulative incidence over time despite declines in mortality; however, given limited follow-up beyond age 65, it is possible that the threshold for breast cancer risk has not been reached in this population. Additionally, even with no change in risk/hazard, there could be an absolute increase in the number of cases among these women over time.

Breast cancer should continue to be tracked in large cohorts of women with HIV to determine if there are trends over a longer time period at older ages. Further investigation

will be required to clarify the role of not only mortality, but also secular trends in the underlying population on breast cancer risk in women with HIV. Comparisons to an appropriate population of women without HIV should be considered to determine if there are disparities by HIV status in breast cancer risk over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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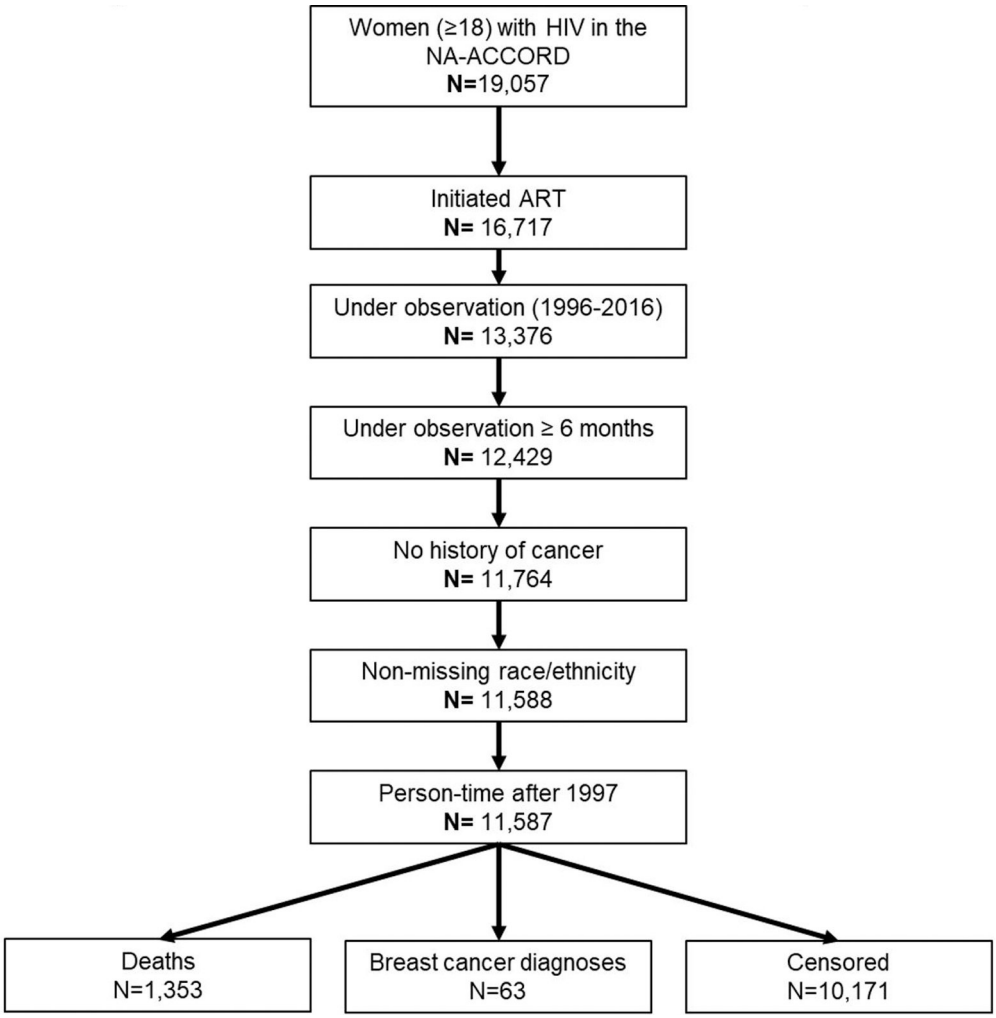


Figure 1.
Flow diagram for inclusion into the analytic study population, NA-ACCORD, 1997–2016

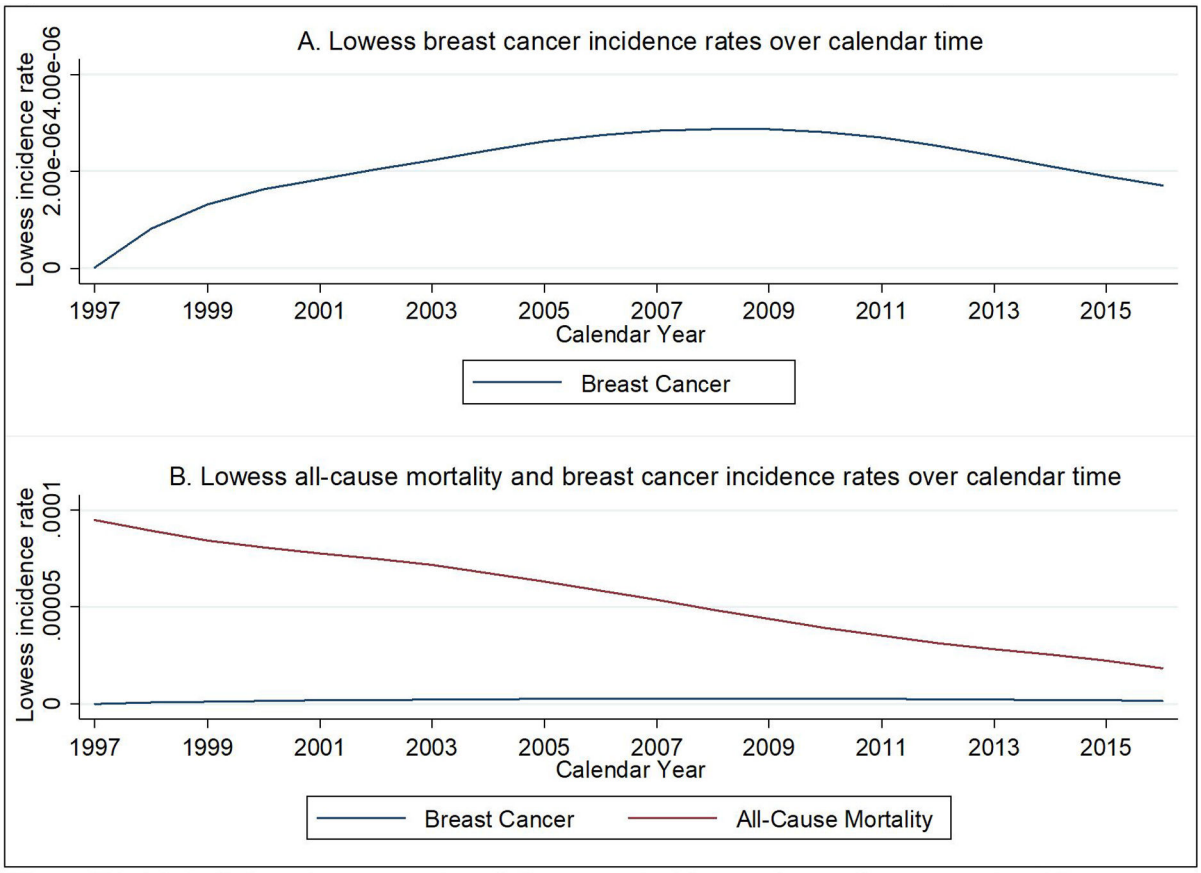
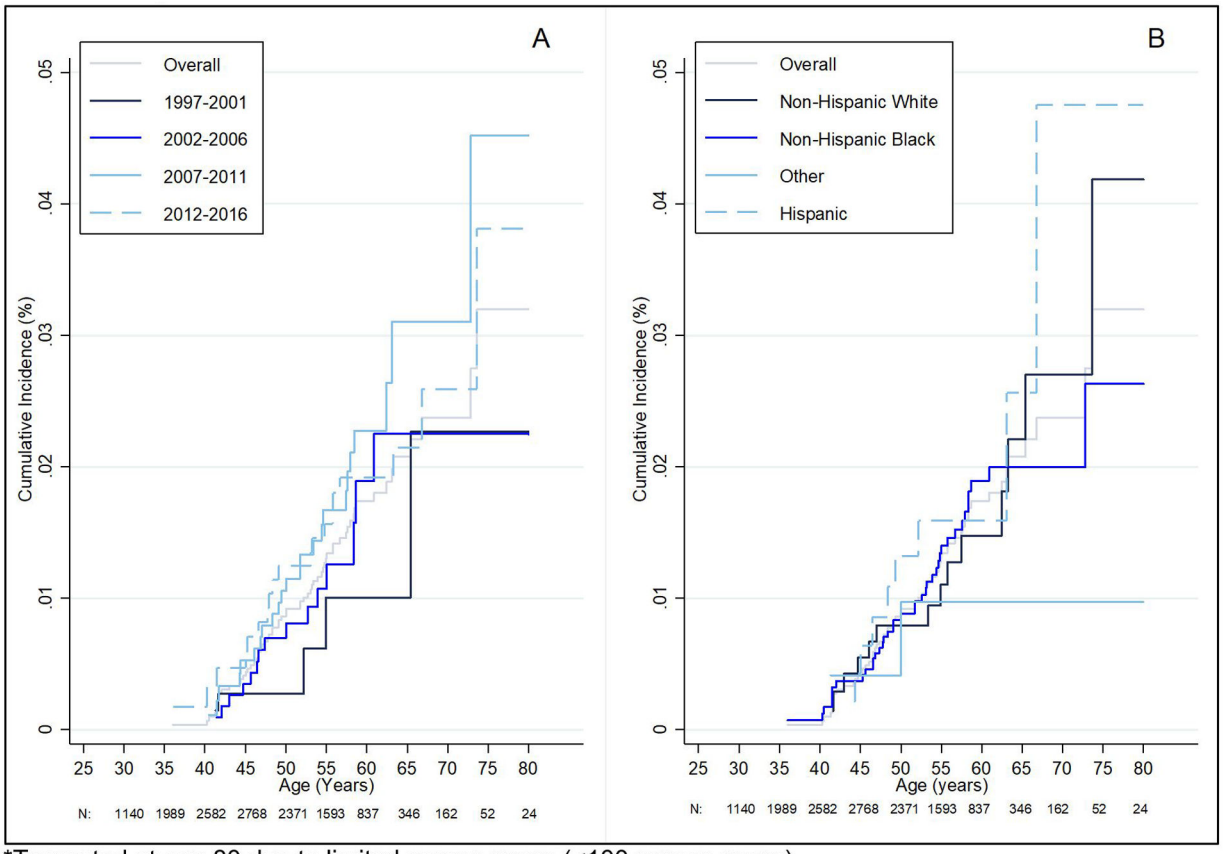


*Figure 2B plots both breast cancer and mortality lowess incidence rates on the same axis, while Figure 2A plots breast cancer rates alone on a magnified Y-axis. The y-axis for Figures 2A and 2B are on different scales.

Figure 2.

Lowess smoothed incidence rates for breast cancer and all-cause mortality over calendar time*



*Truncated at age 80 due to limited person-years (<100 person-years)

Figure 3.

Cumulative incidence of breast cancer over age by calendar period and race/ethnicity (N=11,587), NA-ACCORD, 1997–2016*

Table 1.

Characteristics of women with HIV (N=11,587), NA-ACCORD, 1997–2016

	Median	IQR
Age at entry	40.0	33.5, 47.0
Age at exit	47.0	39.1, 54.1
Calendar year entry	2004	2000, 2010
Calendar year exit	2014	2007, 2016
Follow-up (years)	4.5	2.3, 9.5
	N	**%**
Race/ethnicity		
Non-Hispanic Black	6,887	59.4
Non-Hispanic white	2,313	20.0
Hispanic	1,504	13.0
Other	883	7.6
ADI in the year prior to ART		
No	10,511	90.7
Yes	1,076	9.3
	N	**Rate per 10,000 Person-Years**
Breast cancer	63	8.6
All-cause death	1,353	184.2

Abbreviations: IQR. Interquartile range; ADI, AIDS-defining illness; ART, antiretroviral therapy.

Table 2.

Secular change in breast cancer and death by calendar time

	Cause-specific hazard		Subdistribution hazard	
	csHR*	**95% CI**	**sdHR***	**95% CI**
Breast cancer				
Annual	0.98	0.92, 1.05	1.01	0.94, 1.07
Within periods†				
1997–2001	1.02	0.66, 1.59	1.07	0.68, 1.68
2002–2006	1.00	0.76, 1.33	1.02	0.77, 1.35
2007–2011	0.95	0.77, 1.18	0.97	0.79, 1.20
2012–2016	1.01	0.74, 1.37	1.02	0.75, 1.38
Across periods‡				
1997–2001	ref	--	ref	--
2002–2006	0.76	0.18, 3.32	0.88	0.20, 3.82
2007–2011	0.79	0.22, 2.80	1.01	0.28, 3.61
2012–2016	0.77	0.22, 2.74	1.07	0.30, 3.75
Death				
Annual	**0.89**	**0.87, 0.91**	**0.89**	**0.87, 0.91**
Within periods†				
1997–2001	0.89	0.79, 1.00	0.89	0.79, 1.00
2002–2006	**0.92**	**0.85, 0.99**	**0.92**	**0.85, 0.99**
2007–2011	**0.84**	**0.77, 0.92**	**0.84**	**0.77, 0.92**
2012–2016	0.90	0.77, 1.06	0.90	0.77, 1.06
Across periods‡				
1997–2001	ref	--	ref	--
2002–2006	**0.62**	**0.44, 0.87**	**0.62**	**0.44, 0.87**
2007–2011	**0.37**	**0.26, 0.51**	**0.37**	**0.26, 0.52**
2012–2016	**0.16**	**0.11, 0.24**	**0.16**	**0.11, 0.24**

Abbreviations: cause-specific hazard ratio, csHR; subdistribution hazard ratio (sdHR); CI, confidence interval.

*Adjusted for race/ethnicity and inverse probability weighted for cohort/subsite

†Interpreted as: annual change in breast cancer hazard within the stratum

‡Interpreted as: change in breast cancer hazard over each calendar period compared to 1997–2001

Statistically significant estimates are bolded.